

APPEAL BRIEF

Applicant	:	Charles Allerson, et. al.
App. No	:	10/701,007
Filed	:	November 4, 2003
For	:	Compositions Comprising Alternating 2'-Modified Nucleosides For Use In Gene Modulation
Examiner	:	Jane J. Zara
Art Unit	:	1635

Mail Stop Appeal Brief-Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

In accordance with the notice of appeal filed October 29, 2009, Appellants submit this appeal brief.

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I. REAL PARTY IN INTEREST

Pursuant to 37 C.F.R. 41.37(c)(1), Appellants hereby notify the Board of Patent Appeals and Interferences that the real party in interest is the assignee of record for this application, Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, CA 92008.

II. RELATED APPEALS AND INTERFERENCES

In accordance with 37 C.F.R. § 41.37(c)(1)(ii), Appellants note that notices of appeal have been filed for copending U.S. patent application numbers 11/054,848 and 10/860,265. The claims in those applications are directed to methods and compositions, respectively, that utilize certain double stranded oligomeric compounds.

III. STATUS OF CLAIMS

Claims 1 to 33, 35, 36, 39 to 48, 50 to 52, 63 to 71, 73, 79 to 93, 97 to 103, and 105 have been cancelled without prejudice or disclaimer. Claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 were rejected in an official action mailed July 30, 2009. Accordingly, claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 are the subject of this appeal, and are listed in the claims appendix.

IV. STATUS OF AMENDMENTS

The claims on appeal are those that were submitted in a reply filed with a request for continued examination on June 4, 2009 in response to the final official action mailed December 8, 2008, which claims were examined as reported in the official action mailed July 30, 2009.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of independent claim 34 relates to compositions comprising first and second chemically synthesized oligomeric compounds, wherein the first oligomeric compound is fully complementary to and capable of hybridizing to the second oligomeric compound and to a selected nucleic acid target.¹ Each of the first and second oligomeric compounds is from 12 to 30 linked nucleosides.² At least one of the first and second oligomeric compounds comprises a contiguous sequence of linked nucleosides in which a nucleoside having a 2'-F substituent group

¹ Specification as originally filed at paragraph 39.

² Specification as originally filed at paragraphs 89 to 92.

alternates with a β -D-deoxyribonucleoside, where the 5' nucleoside can be either a nucleoside having a 2'-F substituent group or a β -D-deoxyribonucleoside.³

The dependent claims recite additional chemical features present in the first and/or second oligomeric compounds, including 5'-phosphate groups; 3'-terminal OH groups; conjugate groups; terminal cap moieties; overhangs; and linking groups selected from phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 5'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and boranophosphate.⁴

The dependent claims further recite that the first and second oligomeric compounds are a complementary pair of siRNA oligonucleotides or are antisense and sense oligonucleotides, respectively.⁵

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented to the Board is whether the subject matter of each of the pending claims, 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104, would have been rendered obvious at the time of the invention by Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888 (Elbashir); U.S. patent application publication number U.S. 2004/00180351 (Giese); U.S. patent application publication number U.S. 2003/0143732 (Fosnaugh); and U.S. patent application publication number U.S. 2003/0206887 (Morrissey) in view of the combined teachings of U.S. patent number 6,262,036 (Arnold); U.S. patent application publication number U.S. 2005/0142535 (Damha); and U.S. patent number 6,133,246 (McKay).

VII. ARGUMENT

A. Rejection

Claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Elbashir, Giese, Fosnaugh, and Morrissey in view of the combined teachings of Arnold, Damha, and McKay. The Examiner asserted that

³ Specification as originally filed at paragraphs 32, 41, 44, 45, and 47.

⁴ Specification as originally filed at paragraphs 33, 34, 38, 48, 53, 223, and 224.

⁵ Specification as originally filed at paragraphs 54, 59, and 60.

“[o]ne of ordinary skill in the art would have been motivated to combine the teachings of Elbashir et al, Fosnaugh et al, and Morrissey et al, as applied to modifying and testing the activity of siRNA, with the teachings of McKay, Damha and Arnold, regarding the incorporation of modifications into inhibitory oligonucleotides, for enhancing their ability to bind a target gene and for their ability to enhance oligonucleotide stability, and design the motifs instantly claimed, including alternating 2’-β-D-deoxynucleosides with 2’-modified nucleosides.”⁶ Appellants respectfully submit that the Examiner relied on hindsight to reach this conclusion, and thus failed to properly establish *prima facie* obviousness.

B. Standard

Because obviousness is determined as of the time of the invention, it is fundamental that the Patent Office must not rely on hindsight when assessing obviousness.⁷ In this regard, the Supreme Court recognized in *KSR Int’l Co. v. Teleflex* that “inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.”⁸

Further, the text of § 103 makes clear that the claimed subject matter must be considered “as a whole.”⁹ Courts have warned that a rejection for obviousness cannot be supported by evaluation of the invention “part-by-part.”¹⁰ Accordingly, rejections under § 103 must be supported by “a *reason* that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does*.”¹¹ In applying this legal principle of *KSR* to a case involving chemical compounds, the Federal Circuit held that “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.”¹² Moreover, according to the Federal Circuit “an invention would not be deemed obvious if all that was suggested ‘was to explore a new technology or general approach that

⁶ Office Action dated July 30, 2009 at page 9.

⁷ See e.g., *KSR Int’l Co. v. Teleflex*, 127 S.Ct. 1727, 1742 (2007) (warning against “the distortion caused by hindsight bias . . . and arguments reliant on *ex post* reasoning.”); 35 U.S.C. § 103 (requiring determination of whether an invention “would have been obvious at the time the invention was made.”).

⁸ *Id.*

⁹ 35 U.S.C. § 103(a).

¹⁰ *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004).

¹¹ *Id.* (emphasis added).

¹² *Takeda Chemical Industries, LTD v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007).

seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.”¹³

Finally, as previously held by the Federal Circuit and reiterated by the *KSR* Court, “rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”¹⁴

In the present case, the Examiner has failed to provide credible reasons why one of ordinary skill would have combined particular aspects of the cited references to arrive at the claimed compositions. Instead, the Examiner relies on hindsight to pick and choose elements from the vast, unpredictable, and in some instances contrary, art, to arrive at the claimed subject matter. The Examiner has not considered the claimed invention as a whole and has failed to properly establish *prima facie* obviousness.

C. Analysis

Obviousness is a question of law based upon the following underlying factual inquiries articulated by the Supreme Court in *Graham v. John Deere*: the scope and content of the prior art; the difference between the prior art and the claims; the level of skill in the art; and secondary considerations.¹⁵ Once the *Graham* factual inquiries have been assessed, the Office must determine whether the claimed invention would have been obvious to one of ordinary skill in the art.¹⁶

1. Scope and content of the Prior Art

The Examiner relies on four primary references (Elbashir, Giese, Fosnaugh, and Morrissey) and three secondary references (Arnold, Damha, and McKay).

a) Elbashir

The Examiner contends that Elbashir teaches “methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2’-deoxy and 2’- substitutions” and a “correlation between the placement of 2’-substitutions on the siRNA oligonucleotides and the

¹³ *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007) (citing *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

¹⁴ *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

¹⁵ See *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966).

¹⁶ See, e.g., MPEP § 2142; See also *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (describing *prima facie* case based on “obvious to try combined with a reasonable expectation of success”).

retention of siRNAi activity.”¹⁷ The Examiner’s characterization of Elbashir goes beyond generous.

Elbashir, in fact, describes a total of eight siRNA duplexes in which at least one nucleoside was modified from natural 2’-OH RNA, and all but two of those duplexes were inactive when tested for RNA interference activity. In this regard, the patterns of chemical modifications present in the siRNAs tested for RNAi in the experiments reported in Elbashir, and results of the testing, are summarized below:¹⁸

Motif	Activity
Full RNA (control)	Active
2’-deoxy in two 3’ overhangs of each strand	Active
2’-deoxy in four 3’ nucleosides (2 overhanging and 2 hybridizing) of each strand	“significantly active”
Full 2’-deoxy in either one or both strands	Inactive
Full 2’-O-Me in either one or both strands	Inactive

Contrary to the Examiner’s assertion, Elbashir thus does not broadly teach “methods of target gene inhibition in embryo lysates comprising siRNA molecules comprising 2’-deoxy and 2’- substitutions.” Rather, the article describes only two active siRNA duplexes that comprise 2’-deoxy modifications at either the two 3’-terminal or four 3’-terminal nucleosides. One skilled in the art could not determine from the description provided in Elbashir whether, for example, incorporation of one or more 2’- substituents anywhere in an siRNA duplex would result in active molecules, because the only 2’-substituent-containing duplex tested in the experiments described in Elbashir was inactive in RNAi. Further, contrary to the Examiner’s characterization, Elbashir does not teach a “correlation between the placement of 2’-substitutions on the siRNA oligonucleotides and the retention of siRNAi activity.” Rather, Elbashir merely shows that duplexes containing two or four 2’-deoxy modified nucleosides at the 3’ end were active, and that siRNAs having 2’-deoxy at each position, and 2’-O-methyl at each position,

¹⁷ Office Action dated July 30, 2009 at page 5.

¹⁸ See *Elbashir* at pages 6881-6882 and at Figure 4 at page 6882.

were not. Reporting this result falls far short of teaching a correlation between placement of modifications in siRNA duplexes and retention of RNAi activity. One skilled in the art could not conclude from this result, for example, that placement of the 2'-deoxy modified nucleosides affects activity. For example, the data support the conclusion that four 2'-deoxy substitutions are tolerated, but some greater number of 2'-deoxy substitutions results in inactivity. Indeed, Elbashir speculates that "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." No further guidance regarding number, placement, or type of modifications is provided by Elbashir, however.

b) Giese

The Examiner asserts that "Giese teaches increased siRNA stability from nucleases and increased and sustained target gene inhibition using siRNA with alternating 2' modified residues."¹⁹ Appellants respectfully disagree. The Giese application describes double-stranded ribonucleic acids in which one or both strands comprises a plurality of 2'-modified nucleotides. Groups of such modified nucleotides may be flanked on one or both sides by unmodified ribonucleotides or by modified nucleotides having modifications that differ from those of the other groups of modified nucleotides.²⁰ The application indicates that the modifications are selected from amino, fluoro, methoxy, alkoxy, and alkyl,²¹ but does not discuss compounds having β -D-deoxyribonucleosides, as claimed. The Giese application further recites that the groups of modified, unmodified, or differently modified nucleotides could consist of a single nucleotide.²² The Giese application indicates that in a particular embodiment, both strands of the double-stranded ribonucleic acids comprise 2'-O-methyl modified nucleotides and unmodified ribonucleotides arranged in "an alternating fashion."²³ Figures 15A, 15B, 16A, and 16C of the Giese application depict double-stranded ribonucleic acids in which each strand of the duplexes has 2'-O-methyl modified nucleotides that alternate with unmodified ribonucleotides.

Contrary to the Examiner's assertion, the Giese application does not specifically describe siRNAs with "alternating 2' modified residues." Rather, the Giese application describes siRNA

¹⁹ Office action dated July 30, 2009 at page 8.

²⁰ Paragraph 25.

²¹ Paragraph 34.

²² Paragraph 46.

²³ Paragraph 124.

molecules in which unmodified ribonucleosides alternate with 2' modified ribonucleosides, and the only specific molecule of this type that is described in the Giese application is an siRNA in which both strands have alternating unmodified ribonucleotides and 2'-O-methyl modified ribonucleotides – an siRNA in which *half* of the ribonucleotides are unmodified. Beyond this specific compound, the Giese application includes sweeping language to generally suggest virtually any modification and combination of modifications. Despite the breadth of these general teachings, the Giese application includes no description of incorporating β -D-deoxyribonucleosides into chemically modified siRNAs, as claimed.

Accordingly, based upon the description provided in the Giese application, one skilled in the art could not have determined the effect of including β -D-deoxyribonucleosides, the effect of having no unmodified ribonucleotides, or the effect of alternating 2' modifications (rather than alternating modified/unmodified nucleotides), on siRNA stability or on gene silencing activity at the time of the invention. The Giese application contains no description of such siRNAs, much less an indication of their properties. The Examiner repeatedly refers to the description in the art of various siRNAs having different combinations of different modifications to assert that the presently claimed compounds would have been obvious. But the Examiner offers no explanation as to why the differences between the compounds described in the art and those claimed may be ignored.

c) Fosnaugh and Morrissey

The Fosnaugh and Morrissey applications share a common inventor and assignee, and include substantially overlapping text. For convenience, their disclosures will therefore be discussed together, with differences being noted.

The Examiner asserts that Fosnaugh describes “the effect of different arrangements of various modifications on siRNA ability to bind to an inhibit target gene expression in the presence of RISC,” and further remarks that Morrissey teaches “various ways of designing and optimizing 2'-modifications on siRNA.”²⁴ Again, the Examiner overreaches in characterizing the references. Fosnaugh and Morrissey do not describe with any particularity the effect that different motifs of modifications have on siRNA activity, nor do they teach ways of designing and optimizing chemically modified siRNAs. Instead, Fosnaugh and Morrissey describe vast genres of chemical modifications and broadly discuss oligonucleotides comprising any number

²⁴ Office Action dated July 30, 2009 at page 14.

of such modifications. In addition to this broad discussion, each of these references describes a number of specific, active siRNA molecules. None of the active molecules has a motif of modifications similar to that of the claimed compounds, however. Moreover, beyond repeating the observation reported in Elbashir that 2'-deoxy modifications at the 3' end of siRNAs are tolerated, Fosnaugh and Morrissey provide no further information regarding how the position of chemical modifications in siRNAs affects RNAi activity.

Specifically, Fosnaugh begins with broad generalized teachings, including description of a vast genus of nucleoside modifications. For example, page 5 depicts the structure of the ribose ring of a ribonucleoside in which each position (labeled R3, R4, R5, R6, R7, R8, R10, R11, and R12) may independently be modified with any of an extensive list of possible substituents. Although certain 2'-modifications, including 2'-O-methyl, 2'-deoxy, and 2'-fluoro, are specifically mentioned, Fosnaugh describes countless modifications at every other possible position of the nucleoside.

Fosnaugh continues, discussing the possible numbers of modified nucleosides and/or modified linkages in an oligonucleotide (e.g., about 1 to about 10 or more).²⁵ Notably absent is mention of an siRNA in which each of the nucleosides in one or both strands is modified. In fact, Fosnaugh describes siRNA molecules in which "one or both strand of the siRNA comprise ribonucleotides at positions within the siRNA that are critical for siRNA mediated RNAi in a cell. All other positions within the siRNA can include chemically modified nucleosides."²⁶ Fosnaugh thus teaches that some unmodified RNA nucleosides are necessary for activity. Similar discussion is found in Morrissey at page 13, paragraph 0099. Fosnaugh and Morrissey provide no guidance as to which positions in siRNAs are "critical for siRNA mediated RNAi," and should therefore not be chemically modified, however.

Beyond general statements that do no more than suggest incorporating all known chemical modifications at every possible position in siRNAs (except for the unidentified "critical" ones), Fosnaugh and Morrissey describe certain specific, chemically modified siRNA molecules. None of the specific molecules contains a motif of alternating 2' modifications, however. Moreover, Fosnaugh and Morrissey describe a synthesis strategy that involves modifying each nucleoside of a particular base type; that is, each pyrimidine or purine comprises

²⁵ See page 7.

²⁶ Fosnaugh at page 9, paragraph 0069.

the same modification, or no modification, throughout the oligonucleotide. As a result, each adenosine of a particular oligonucleotide has the same modification throughout the oligonucleotide, as does each cytosine, etc. Consequently, using the technique of Fosnaugh/Morrissey, the pattern of modifications present in an siRNA depends entirely on the base sequence of the oligonucleotides present in the siRNA duplex. This sequence-dependent substitution scheme teaches by implication that the pattern or placement of modifications within an siRNA is not critical. Rather, Fosnaugh and Morrissey suggest that what matters is the base sequence of the oligonucleotides. Accordingly, not only do the Fosnaugh and Morrissey references fail to teach alternating patterns of 2' modifications, they do not discuss other motifs or even the concept of motifs or patterns of chemical modifications. Instead, the pattern of modifications is a matter of chance, dictated by the nucleobase sequence of the particular oligonucleotides present in the siRNAs.

d) Primary References Combined

The Examiner contends that the combination of the primary references demonstrate “the importance of routinely testing the placements and types of modifications on siRNA, and the effects of these modifications and their locations on the siRNA molecule on oligonucleotide stability, target binding and the inhibitory capabilities of siRNA.”²⁷ Applicants submit that the references actually demonstrate the unpredictability and absence of meaningful guidance in designing such molecules. The combined primary references describe a vast number of chemical modifications that can be incorporated at any position of the ribose ring of nucleosides present in siRNAs; that certain numbers of particular modified nucleosides within siRNAs are tolerated, such as two or four 2'-deoxy nucleosides at the 3'-ends of both strands of an siRNA, and 2'-O-methyl modifications that alternate with unmodified nucleosides in both strands of an siRNA molecule; that certain other patterns of chemical modifications, such as 2'-deoxy modifications at each position, and 2'-O-methyl modifications at each position, in either or both strands of an siRNA, abolishes RNAi activity; and that some number of unmodified ribonucleosides at unidentified positions in siRNAs appear to be necessary or “critical” for retaining RNAi activity. Significantly, this collection of information falls far short of teaching the effect that the type and placement of chemical modifications in siRNA molecules has on the molecules' stability, target binding affinity, and inhibitory activity, as asserted by the Examiner.

²⁷ Office Action dated July 30, 2009 at page 12.

The primary references also discuss some of the goals of introducing chemical modifications into siRNA molecules. For example, Elbashir notes that “2’-deoxy modifications may reduce costs of RNA synthesis and may enhance RNase resistance.”²⁸ Fosnaugh/Morrissey aspire to use modifications to “overcome potential limitations of in vivo stability and bioavailability inherent to native RNA molecules . . . enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect . . . longer half-life in serum . . . improving cellular uptake . . . minimize the possibility of activating interferon activity.”²⁹ Notably, the references do not describe or suggest specific ways to achieve these goals, however, and certainly do not suggest producing siRNAs having the claimed motifs of chemical modifications. Moreover, the references do not teach how to balance such goals when designing oligomeric compounds when, for example, a particular motif or modification improves the fitness of a compound in one respect, but detracts from it with respect to another. The full 2’-O-methyl compounds described in Elbashir, for example, likely have improved stability and affinity for a target RNA, but they are reported to have no activity, thus making them unsuitable for use as siRNAs.

e) Secondary References (Arnold, Damha, and McKay)

The Examiner attempts to fill the substantial gaps left by the primary references by relying on three secondary references, each of which describes single-stranded antisense oligonucleotides that reduce target RNA through a pathway that requires RNase H activity. RNase H is an enzyme that cleaves the RNA strand of DNA/RNA duplexes. Accordingly, antisense oligonucleotides that reduce target RNA by acting as substrates for RNase H must mimic a DNA strand, and such compounds were known at the time of present invention to have certain structural requirements. In this regard, a stretch of 2’-deoxy, or DNA-like, nucleosides was known to be required in RNase H-dependent antisense oligonucleotides. And particular chemical modifications described in the cited references were known to improve certain properties of RNase H-dependent antisense compounds, provided that the fundamental requirement of DNA or DNA-like nucleosides was preserved. For example, one motif of chemical modifications described in the secondary references is a “gapmer,” which comprises a central region of 2’-deoxy nucleosides flanked on each side by regions of modified nucleosides.

²⁸ Elbashir at page 6885.

²⁹ Fosnaugh at paragraph 0035; Morrissey at paragraph 0052.

Elbashir, Giese, Fosnaugh, and Morrissey describe oligonucleotide duplexes that are suitable for reducing target RNA through the RNA interference (RNAi) pathway. Not surprisingly, the structural requirements of substrates utilized in this pathway differ from the structural requirements of substrates for RNase H. In this regard, the active compounds described in Elbashir, Giese, Fosnaugh, and Morrissey are double-stranded compounds that comprise at least some unmodified RNA nucleosides, while the active compounds described in Arnold, Damha, and McKay are single-stranded oligonucleotides that have a region of 2'-deoxy or DNA-like nucleosides.

The RNAi and RNase H-dependent pathways for reducing target RNA are sufficiently different that there would have been no reason for those skilled in the art to have believed at the time of the invention that the types and patterns of chemical modifications beneficial for the substrates utilized in one pathway would be also be beneficial for the substrates utilized in the other. If those skilled in the art were, nevertheless, to have looked to the chemical modifications reported as being beneficial for RNase H substrates, such as DNA-containing gapmers, and were to have incorporated such modifications into RNAi substrates, the resulting compounds would not have been active in RNAi (and are not the subject of the present application).

(1) Arnold

Arnold describes chemically modified antisense oligonucleotides used as substrates for RNase H. Specifically, Arnold contains extensive description of antisense oligonucleotides that contain modified internucleoside linkages and indicates that the modified linkages may be present in the oligonucleotides in combination with other modifications, such as 2' modifications. In this regard, Arnold describes oligonucleotides that contain both modified linkages and 2'-sugar modifications, and example 34 describes particular antisense oligonucleotides having alternating linkage modifications and uniform 2'-modifications.³⁰ Arnold indicates that such patterns of chemical modifications may be beneficial for RNase substrates, but nothing in the reference teaches or suggests that such modifications would be desirable in siRNA molecules.

³⁰ See Col. 49 (noting that "where 2'-deoxy or 2'-O-methyl substitutions are indicated below, these structures occur on all of the residues in the alternating or repeated sequence.").

(2) Damha

Damha describes the incorporation of arabinonucleosides, including 2' arabino fluoro nucleosides (FANA), into single-stranded antisense oligonucleotides that elicit RNase H activity. FANA, as described in Damha is "DNA-like" in its conformation.³¹ Damha thus teaches that oligonucleotides containing DNA and FANA, which are uniformly DNA-like, act as RNase H substrates. Significantly, Damha lacks any teaching that would facilitate the design of siRNAs.

(3) McKay

McKay describes a vast number of types and patterns of chemical modifications said to be beneficial for single-stranded antisense oligonucleotides utilized in RNase H-dependent methods for reducing target RNA. Patterns of chemical modifications described in McKay include gapmers, wingmers, hemimers, and fully modified oligonucleotides. McKay does not describe patterns of alternating modifications, and contains no teaching or suggestion regarding the types and patterns of chemical modifications that would be beneficial for siRNA molecules.

2. Comparison of the Claims with the Cited Art

The cited references fail to describe or suggest oligomeric compounds that comprise alternating 2'-F modified ribonucleosides and β -D-deoxyribonucleosides, as claimed. As discussed above, Elbashir, Giese, Fosnaugh, and Morrissey describe a small number of chemically modified siRNAs. Elbashir tested fully 2'-modified siRNAs and found them to be inactive in RNAi, but two to four 2'-deoxynucleotides were tolerated at the 3' end of siRNAs. Giese describes active siRNAs in which both strands have alternating unmodified and 2'-O-methyl modified ribonucleotides, but contains no description of siRNAs in which each nucleoside of at least one of the strands is modified at the 2' position. Fosnaugh and Morrissey generically discuss varying the number of modified nucleosides in siRNAs, but do not describe with specificity where the modified nucleosides should be placed in siRNAs to yield active molecules. In fact, by linking modifications to nucleobase type, Fosnaugh and Morrissey suggest that the position of modifications within siRNAs need not be considered when designing chemically modified siRNAs.

Moreover, Elbashir, Giese, Fosnaugh, and Morrissey each indicate that some unmodified RNA nucleosides are necessary for siRNA activity. In contrast, the present claims recite duplexes in which each nucleoside of at least one strand is modified at the 2' position. In

³¹ See e.g., page 15.

this regard, as understood by those skilled in the art, β -D-deoxyribonucleosides are “DNA-like” due to the presence of a hydrogen atom, rather than an -OH group, at the 2' position, and β -D-deoxyribonucleosides thus constitute modified nucleosides when present in RNA molecules. Since at least one strand of the claimed duplexes comprises alternating 2'-F modified ribonucleosides and β -D-deoxyribonucleoside, the claimed oligomeric compounds lack the “critical” unmodified ribonucleosides described in Fosnaugh. Significantly, not a single active compound described in Elbashir, Giese, Fosnaugh, or Morrissey is fully modified at the 2' position. And the only compounds that are fully modified (i.e., have no natural 2'OH RNA nucleosides) were inactive in RNAi. The combined teachings of Elbashir, Giese, Fosnaugh, and Morrissey therefore do not suggest siRNA molecules having a strand of alternating 2'-modifications, and actually teach away from compounds that lack any unmodified RNA nucleosides by reporting that such compounds are inactive in RNAi, and indicating that unmodified ribonucleosides are necessary for RNAi activity.

The three secondary references relied upon by the Examiner describe chemically modified antisense oligonucleotides utilized as substrates in RNase H-dependent methods for reducing target RNA, and therefore do not compensate for the deficiencies of the primary references because they lack any teaching regarding chemically modified siRNAs. As discussed above, RNase H substrates must have a stretch of DNA or DNA-like nucleosides. The Examiner has failed to provide sufficient reasons why one of skill in the art would have combined references describing methods that utilize RNase H activity with references describing siRNA-based methods. Instead, the Examiner glosses over this distinction, remarking that “[o]ne of ordinary skill in the art would have been motivated to combine the teachings of Elbashir et al, Fosnaugh et al and Morrissey et al, as applied to modifying and testing the activity of siRNA, with the teaching by McKay, Damha and Arnold regarding the incorporation of modifications into inhibitory oligonucleotides, for enhancing their ability to bind a target gene and for their ability to enhance oligonucleotide stability, and design the motifs instantly claimed, including alternating 2'- β -D-deoxyribonucleosides with 2'-modified nucleosides.”³² In making this statement, the Examiner trivializes the significant differences in the two biological mechanisms and the resulting differences in the structural requirements of the substrates that are dictated by the mechanisms.

³² Office Action dated July 30, 2009 at page 9.

As noted above, antisense oligonucleotides that reduce target RNA by acting as substrates for RNase H are single stranded and comprise at least four contiguous DNA or DNA-like nucleosides. Elbashir teaches that siRNAs having oligonucleotides that are uniformly DNA-like in each nucleoside of either or both strands are inactive in RNAi. Damha describes antisense oligonucleotides that comprise alternating 2'-deoxy and F-arabino (FANA) nucleosides. FANA nucleosides are similar in conformation to DNA, so the compounds described in Damha are actually uniformly DNA-like in character, and such compounds were shown by Elbashir to be inactive in RNAi. There would therefore have been no reason at the time of the invention for those skilled in the art to have combined teachings from Elbashir and Damha.

3. Level of Ordinary Skill in the Art

The level of skill in the art of molecular biology and in the art medicinal chemistry is high. As articulated in *KSR*, a person of ordinary skill is “also a person of ordinary creativity and not an automaton.”³³

4. Rationales Supporting a Conclusion of Obviousness

Procedurally, the examiner has the initial burden of establishing *prima facie* obviousness. Only if that burden is met, must applicants then present evidence of secondary considerations to overcome a finding of obviousness.³⁴ As indicated by the *KSR* Court, to establish *prima facie* obviousness, the examiner must provide “reason(s) why the claimed invention would have been obvious.”³⁵ In the context of a chemical invention, “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound.”³⁶ In the present case, to establish *prima facie* obviousness, the Examiner appears to have relied on the standard of obvious to try combined with a reasonable likelihood of success. The Examiner has failed to establish either prong of this test, however.

(1) Obvious to Try the Claimed Invention

The claimed compositions comprising oligomeric compounds having a pattern of alternating 2'-modifications would not have been obvious to try at the time of the invention,

³³ *KSR* at 1742.

³⁴ See *In re Oetiker* 977 F.2d 1443, 1445 (Fed. Cir. 1992); MPEP § 2142.

³⁵ *Id.*

³⁶ *Takeda* at 1356.

which the M.P.E.P. describes as “choosing from a finite number of identified, predictable solutions.”³⁷ The Examiner comments that “[i]t would have been obvious to incorporate various motifs and configurations of 2’-modifications...into siRNA molecules for enhancing their target binding and stability, yet minimizing inactivation of the siRNA ability to inhibit target gene expression.”³⁸ The Examiner does not indicate, however, which of these “various motifs and configurations” those skilled in the art would have tried. Indeed, the Examiner remarks that those of skill in the art “would have produced various motifs as a matter of design choice and optimizing 2’-modified motifs within the siRNA while maintaining its siRNA activity would have been a matter of design choice after testing various modifications and their combinations.”³⁹ Since the Examiner failed to identify any description or suggestion in the art of siRNAs having the particular patterns of chemical modifications claimed, it appears that the Examiner contends that it would have been obvious to try all possible types and combinations of modifications until ultimately arriving at the claimed patterns of modifications. That position is untenable, however, and cannot support a rejection under § 103(a).

(a) Finite number

In *KSR*, the Supreme Court noted that when “there are a finite number of identified predictable solutions a person of ordinary skill has good reason to pursue the known options in his or her technical grasp.”⁴⁰ *KSR* involved simple technology with only a few variables; a control pedal and an electronic throttle, each of which was separately known in the art. In *Takeda*, though, the inventors selected a lead compound from among several hundred for modification and further investigation. In finding non-obviousness, the *Takeda* Court contrasted the technology involved from that in *KSR*, remarking that, “[r]ather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation.”⁴¹ Similarly, the invention in *Ortho McNeil Pharmaceuticals v. Mylan Laboratories*, an epilepsy

³⁷ *Id.*

³⁸ Office Action dated July 30, 2009 at pages 7 to 8.

³⁹ *Id.* at pages 9 to 10.

⁴⁰ *KSR* at 1742.

⁴¹ *Takeda* at 1359.

drug, did “not present a finite (and small in the context of the art) number of options easily traversed to show obviousness.”⁴²

Likewise, the pattern of chemical modifications present in the claimed oligomeric compounds is only one of a vast number of possible patterns of modifications that could have been incorporated into siRNAs at the time of the invention. Fosnaugh describes nucleosides having chemical modifications at every position of the sugar ring⁴³, and nucleosides comprising such modifications could be arranged in a virtually infinite number of possible patterns in each of the two strands of siRNA compounds of varying lengths. In contrast, the present claims recite complementary oligomeric compounds having a specific motif of chemical modifications - alternating 2'-F modified ribonucleosides and β -D-deoxyribonucleosides on at least one strand of the duplexes. The Examiner has offered no credible reason why those skilled in the art would have selected this particular pattern of 2'-modifications from among the limitless number of possible patterns and combinations of modifications described in the cited art. This alone defeats the Examiner's contention that the claimed compositions would have been obvious.

(b) Predictable Solutions

The rejection must also fail because the efficacy of the claimed oligomeric compounds in RNAi was not reasonably predictable at the time of invention. As noted, the Examiner's solution to the vast teaching in the art would have been to try all possible combinations of chemical modifications. Not only would such an approach have been impossible, given the vast number of types and combinations of chemical modifications known in the art, it also fails to provide proper grounds for an obviousness rejection because the art does not support a conclusion that the claimed compounds were selected from among predictable solutions to the problem of designing active chemically modified siRNAs.

In *KSR*, once the claimed control pedal was designed, there was little doubt that it would work for its intended purpose. Thus, as the Supreme Court noted, the claimed invention was selected from among “predictable solutions.” In *Takeda*, though, the lead compound, which was selected from several hundred for further optimization, was modified in two ways with unpredictable results. To arrive at the claimed compound from the identified lead, a methyl group was substituted with an ethyl group, and the resulting ethyl group was moved from one

⁴² 520 F.3d 1358, 1364 (Fed. Cir. 2008).

⁴³ See, for example, paragraphs 39 and 40.

position on a ring to another. Although these were routine modifications readily performed by those of ordinary skill, the court found nothing in the art that would have suggested how such modifications would affect the activity of the resulting compounds, much less suggest that “performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin.”⁴⁴ Until the compound was made and tested, its properties could not have been reasonably predicted. Similarly, the invention in *Sanofi-Synthelabo v. Apotex* was an isolated enantiomer of a known racemate, about which an expert testified that “no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity.”⁴⁵ Accordingly, the Federal Circuit upheld a finding of non-obviousness, noting that “a person of ordinary skill in this field would not reasonably have predicted that the dextrorotary enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity.”⁴⁶

The issue in the present case is thus whether the effect of the combination of chemical modifications present in the claimed compounds would have been predictable (like the simple electronic control throttle in *KSR*) or unpredictable (like the chemical modifications in *Takeda* or the enantiomers in *Sanofi-Synthelabo*). The Examiner has offered no reason why such chemical modifications would have been reasonably predicted to yield active siRNA compounds. Instead, the Examiner relies on art indicating that siRNA molecules having alternating 2' modified ribonucleosides with unmodified ribonucleosides in both strands are active in RNAi, while providing no evidence that siRNAs having at least one strand fully modified at the 2' position are active in RNAi. The Examiner further relies on evidence that certain nucleoside modifications can provide benefits for single-stranded antisense oligonucleotides that reduce target RNA by acting as substrates for RNase H. Not only is such reliance scientifically unsound, it would likely have lead to the production of inactive compounds. For example, even if those skilled in the art could safely have assumed that chemical modifications beneficial for RNase H-dependent antisense oligonucleotides would provide similar benefits for siRNAs, such artisans would still have had to determine where to place the modifications within siRNA molecules. For antisense oligonucleotides, a commonly used motif is a ‘gapmer’ that comprises modified nucleosides in

⁴⁴ *Id.*

⁴⁵ 550 F.3d 1075, 1087 (Fed. Cir. 2008) .

⁴⁶ *Id.*

the end regions, or wings, flanking a central region of deoxynucleosides.⁴⁷ Oligomeric compounds comprising such a gapmer motif are unsuitable in siRNAs, however. To this end, the Examiner does not explain how those of skill in the art would have known which portions of the art to utilize and which portions to disregard when designing siRNA compounds.

As in *Takeda*, *Sanofi*, and *Ortho-McNeil*, the art of siRNA design at the time of the invention was unpredictable. Since those of ordinary skill in the art could not have reasonably anticipated which motifs of chemical modifications would yield siRNAs active in RNAi, the invention represents a selection from among a vast number of unpredictable possible choices, and is therefore non-obvious. In this regard, the references cited by the Examiner actually discuss some of the complicating and often competing goals of siRNA production.⁴⁸ The Examiner dismisses the complexity of siRNA design, however, by remarking that certain modifications can yield siRNAs having desirable properties, and apparently concluding that all types and patterns of modifications would therefore have been obvious. Omitted from that conclusion is the complicated, unpredictable reality that improving any one property of an siRNA may detract from another of the molecule's properties. For example, the siRNAs fully modified with 2'-O-methyl groups at each position described in Elbashir would have been expected to have had desirable resistance to nucleases and to have had high affinity for target messenger RNA. However, Elbashir reports that such compounds were inactive in RNAi, making them unsuitable as siRNAs. Many variables influence whether a particular motif of chemical modifications will yield active siRNA molecules with beneficial properties. In the setting of such unpredictability, the Examiner has failed to provide a reasonable basis for those skilled in the art to have selected the particular motifs of modifications present in the claimed compounds, and the Examiner actually dismisses the complexity of siRNA design, blithely labeling it "optimization" or "design choice."⁴⁹ In reality, balancing the competing properties of siRNAs has proven to be unpredictable and extremely challenging.⁵⁰

⁴⁷ See e.g., McKay, Col. 11, lines 32 to 64 and Tables 11, 12, 14, 19, 21, 24, and 26.

⁴⁸ See, for example, Fosnough at paragraph 0035 (discussing the competing desirability of improving stability, bioavailability, and activity).

⁴⁹ Office action dated July 30, 2009 at pages 14 to 15.

⁵⁰ See, for example, Chiu *et. al.*, *RNA*, 2003, 9, 1034-1048; Czauderna, *et. al.*, *Nucleic Acid Res.*, 2003, 31(11), 2705-2716, copies of which are attached in Appendix IX. Appellants note that some of the cited scientific literature was published after the filing date of the present application. Although post-filing art cannot support an argument of "teaching away," it is cited here to demonstrate that the art was unpredictable at the time of invention, and remained unpredictable even after the present application was filed.

Moreover, the references cited by the Examiner actually describe inactive compounds, such as the siRNAs fully modified with 2'-O-methyl groups described in Elbashir. The Examiner conveniently, but improperly, relies on the description of the active compounds to suggest that siRNA design is predictable, while ignoring the inactive compounds. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggest to one of ordinary skill in the art."⁵¹ If active compounds suggest that other compounds having the same or very similar chemical modifications will likewise be active, then inactive compounds must suggest the opposite for compounds having the same or very similar modifications. When "prior art contains apparently conflicting references, the [Patent Office] must weigh each reference for its power to suggest solutions to an artisan of ordinary skill."⁵² When one considers the field on balance, it becomes clear that chemical modifications are neither universally beneficial nor detrimental for siRNAs. Rather, the art teaches that modifications may provide benefits or detriments depending on their type, number, and placement within siRNA molecules. As in *Takdea* and *Sanofi*, at the time of filing, there was no known scientific principle that allowed reasonable prediction of which motifs of modification would yield active compounds and which would not. Such a level of unpredictability in the art is incompatible with a finding of obviousness.

(2) Reasonable Expectation of Success of the Claimed Invention

Even if there were only a finite number of possible patterns of chemical modifications that could be incorporated into siRNAs, and even if the art were reasonably predictable with respect to the effect of such chemical modifications, neither of which is actually the case, the rejection for alleged obviousness is still groundless due to lack of a reasonable expectation of success. The Examiner has failed to provide reasons why those of ordinary skill in the art, having designed the complementary oligomeric compounds bearing the alternating pattern of chemical modifications recited in the claims, would have had a reasonable expectation that the duplexes would reduce target messenger RNA.

⁵¹ *In re Wesslau* 53 C.C.P.A. 746, 750 (1965); see also *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (holding that the district court improperly ignored portions of a reference that led away from obviousness).

⁵² *In re Young* 927 F.2d 588, 591 (Fed Cir. 1991).

Instead, the Examiner improperly asserts that if the claimed compounds could have been made and tested using routine skill, then the compounds themselves would have been obvious, stating that “[o]ne of ordinary skill would have expected that the incorporation of these modifications are optimized using routine experimentation because Damha, McKay and Arnold all teach optimization experiments where antisense oligonucleotides comprising an array of different combinations of these well known modifications are tested for their ability to target and bind target genes and inhibit their expression, the ability to incorporate the modifications claimed were well known in the art, and testing different motifs was very routine at the time the instant invention was made.”⁵³ Significantly, however, whether or not methods of making and testing chemically modified siRNAs were routine in the art at the time of the invention has no bearing upon whether the molecules themselves would have been obvious at that time, due to the inability to reasonably predict whether the modified siRNAs would have exhibited RNAi activity.

For example, the experimentation required to make the chemical modifications to the lead compound at issue in *Takeda* was merely routine, as were the assays used to assess the resultant compound’s activity. The Federal Circuit nevertheless found that the compound would not have been obvious, as discussed above, due to the unpredictability of the effect of the modifications on the compounds’ activity and characteristics. The routine nature of making and testing new compounds does not make selection from among an infinite number of unpredictable possibilities obvious. Nor do routine methods of making and testing new chemical compounds create an expectation that particular compounds will be active and exhibit beneficial properties, but instead merely provide a way to determine whether success in these areas has been achieved. Indeed, the ease or difficulty of testing the compounds is not logically connected to the obviousness of the compounds. The Examiner also seems to suggest that if the invention were the result of trial and error, where the inventors made and tested many siRNA molecules each having one of many different combinations of chemical modifications, then the resulting compounds would have been obvious. This is not the law, however.⁵⁴ The question is not whether those skilled in the art would have reasonably expected to have been able to produce chemically modified siRNAs and test them for RNAi activity at the time of the invention.

⁵³ Office Action dated July 30, 2009 at page 9.

⁵⁴ See e.g., 35 U.S.C. § 103 (stating, “[p]atentability shall not be negated by the manner in which the invention was made.”).

Rather, the question is whether there would have been a reasonable expectation that the particular chemically modified complementary oligomeric compounds recited in the claims would have been active in RNAi before Appellants' invention. The Examiner has failed to provide any reason for such an expectation.

Finally, although it should be apparent, Appellants note that the present case is quite different from the circumstances at issue in *In re Kubin*.⁵⁵ In that case, the Federal Circuit found that a nucleic acid sequence was obvious in view of art disclosing the partially purified protein encoded by the nucleic acid and known cloning and sequencing techniques.⁵⁶ In *Kubin*, the goal of the research was to identify the single, naturally occurring, nucleic acid sequence encoding a known protein. The court held that given the state of the art, one of ordinary skill would reasonably have expected to succeed and to correctly identify the sequence. In the present case, however, the inventors designed new compounds from an infinite number of theoretical possibilities. Some unknowable sub-set of those theoretical possibilities (or none of them) might have been active as siRNA compounds, while others (or all of them) could have been inactive. Since those skilled in the art could not have predicted in advance which, if any, would be active, there was no reasonable expectation that the claimed compounds would succeed. The claimed oligomeric compounds did not result from simple characterization of a single, naturally occurring molecule, as in *Kubin*. Rather, the inventors created new compounds, previously unknown in nature, from among an infinite number of possibilities, and then determined whether the compounds possessed properties that could not have been reasonably predicted, as in *Takeda*. Although routine techniques may have been used in undertaking such research, such experimentation would not have created an expectation that the resultant compounds would have been active in RNAi, and, accordingly, would not have rendered the compounds obvious. Indeed, the *Kubin* opinion considers such a circumstance, noting that “where a defendant merely throws metaphoric darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.”⁵⁷

⁵⁵ 561 F.3d 1351 (Fed. Cir. 2009).

⁵⁶ See *Kubin* at 1360 (explaining that “this court cannot deem irrelevant the ease and predictability of cloning the gene that codes for that protein.”).

⁵⁷ *Kubin* at page 1359.

4. Hindsight

The Examiner asserts that when designing oligomeric compounds for reducing target mRNA, it would have been obvious to start with double stranded siRNA, as described in Elbashir and Fosnaugh. Next, the Examiner asserts that it would have been obvious to chemically modify the siRNA by selecting 2'-modifications from among a vast number of possible chemical modifications described in Fosnaugh, Morrissey, and Giese. And the Examiner further contends that when designing such siRNAs it would have been obvious to consider art describing beneficial chemical modifications for RNase H-dependent single-stranded antisense oligonucleotides, even though such modifications might abolished RNAi activity. The Examiner maintains that it would then have been obvious to arrange the 2'-modifications in the siRNAs in any of a nearly infinite number of possible combinations. The Examiner indicates that routine experimentation could then have been used to determine which of these chemically modified siRNAs were active in RNAi, which would have resulted in production of the claimed compounds having alternating 2'-modifications in at least one strand.

The Examiner contends that the efficacy of the claimed, chemically modified oligomeric compounds for reducing target mRNA would have been reasonably predictable at the time of the invention, even though the art did not provide a basis for such a prediction and taught that many combinations of chemical modifications yield siRNAs that are inactive in RNAi. Finally, the Examiner contends that those skilled in the art would have reasonably expected that complementary oligomeric compounds having the particular chemical modifications recited in the claims would have successfully reduced target messenger RNA, despite the absence of any articulated reason for such an expectation, beyond an assertion that success could have been achieved using known methods for synthesizing siRNAs and testing them for biological activity.

Throughout, the Examiner improperly shifts the analysis from alleged obviousness of the claimed invention to alleged obviousness of inventive activities that could lead to the claimed invention. The Examiner mistakenly relies on the logic that if there is a reasonable expectation that an inventive undertaking will succeed, then the specific inventions arising from that undertaking are obvious. However, where there are an infinite number of unpredictable solutions with no reasonable expectation that any particular solution will be successful, obviousness cannot be established merely by showing the inventive undertaking was reasonable.

If obviousness could be established under such circumstances, patents would only be available for inventions resulting from unreasonable investment.

Appellants urge that the Examiner has “simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention . . . was obvious.”⁵⁸ As articulated by the Federal Circuit, “this reasoning is always inappropriate for an obviousness test.”⁵⁹ Accordingly, the Examiner has failed to establish *prima facie* obviousness.

D. Conclusion

For the above reasons, Appellants respectfully request that the Board reverse the Examiner’s rejection of the pending claims under 35 U.S.C. § 103(a).

Respectfully submitted,

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/Jane E. Inglese/
Jane E. Inglese, Ph.D.
Registration No. 48,444

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

⁵⁸ *Ortho-McNeil v. Mylan Labs.* at 1364.

⁵⁹ *Id.*

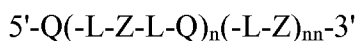
VIII. CLAIMS APPENDIX

1-33. (Canceled)

34. (Previously presented) A composition comprising first and second chemically synthesized oligomeric compounds, wherein:

the first oligomeric compound is fully complementary to and capable of hybridizing with said second oligomeric compound and to a selected nucleic acid target;

at least one of said first and second oligomeric compounds comprises a contiguous sequence of linked nucleosides wherein the sequence defines an alternating motif having the formula:



wherein:

each L is an internucleoside linking group;

each Q is a nucleoside having a 2'-F substituent group and each Z is a β -D-deoxyribonucleoside; or

each Q is β -D-deoxyribonucleoside and each Z is a nucleoside having a 2'-F substituent group;

n is from about 8 to about 14 and nn is 0 or 1; and

each of said oligomeric compounds is from 12 to 30 linked nucleosides in length.

35-36. (Canceled)

37. (Previously presented) The composition of claim 34 wherein only one of said first and said second oligomeric compounds comprises said alternating motif.

38. (Previously presented) The composition of claim 34 wherein both of said first and said second oligomeric compounds independently comprise said alternating motif.

39-48. (Canceled)

49. (Previously presented) The composition of claim 34 wherein each Z is a β -D-deoxyribonucleoside.

50-52. (Canceled)

53. (Original) The composition of claim 34 wherein said first oligomeric compound further comprises a 5'-phosphate group.

54. (Original) The composition of claim 34 wherein said second oligomeric compound further comprises a 5'-phosphate group.

55. (Original) The composition of claim 34 wherein each of said first and said second oligomeric compounds independently, comprise a 5'-phosphate group.

56. (Original) The composition of claim 34 wherein said first oligomeric compound comprises a 3'-terminal OH group.

57. (Original) The composition of claim 34 wherein the nucleosides of each of said first and said second oligomeric compounds are linked by phosphodiester internucleoside linking groups.

58. (Original) The composition of claim 34 wherein the nucleosides of each of said first and said second oligomeric compounds are linked by phosphorothioate internucleoside linking groups.

59. (Original) The composition of claim 34 wherein the nucleosides of one said first and said second oligomeric compound are linked by phosphorothioate internucleoside linking groups and the nucleosides of the other of said first and said second oligomeric compound are linked by phosphodiester internucleoside linking groups.

60. (Original) The composition of claim 34 wherein the nucleosides of said first oligomeric compound are linked by phosphorothioate internucleoside linking groups and the

nucleosides of said second oligomeric compound are linked by phosphodiester internucleoside linking groups.

61. (Original) The composition of claim 34 wherein each of the nucleosides of said first and said second oligomeric compound are independently linked by phosphorothioate or phosphodiester internucleoside linking groups.

62. (Original) The composition of claim 34 wherein each of the nucleosides of said first and said second oligomeric compound are independently linked by an internucleoside linking group selected from the group consisting of phosphodiester, phosphorothioate, chiral phosphorothioate, phosphorodithioate, phosphotriester, aminoalkylphosphotriester, methyl phosphonate, alkyl phosphonate, 5'-alkylene phosphonate, chiral phosphonate, phosphinate, phosphoramidate, 3'-amino phosphoramidate, aminoalkylphosphoramidate, thionophosphoramidate, thionoalkylphosphonate, thionoalkylphosphotriester, selenophosphate and boranophosphate.

63-71. (Canceled)

72. (Original) The composition of claim 34 further comprising at least one conjugate group.

73. (Canceled)

74. (Original) The composition of claim 34 wherein at least one of said first and said second oligomeric compounds further comprises at least one terminal cap moiety attached at the 3'-end, the 5'-end or both the 3'-end and the 5'-end.

75. (Original) The composition of claim 74 wherein said terminal cap moiety is an inverted deoxy abasic moiety.

76. (Original) The composition of claim 74 wherein one of said first and second oligomeric compounds is a sense strand and wherein said sense strand comprises a terminal cap moiety at one or both of the 3'-terminal and the 5'-terminal ends.

77. (Original) The composition of claim 76 wherein said terminal cap moiety is an inverted deoxy abasic moiety.

78. (Previously presented) The composition of claim 34 wherein said first and said second oligomeric compounds are a complementary pair of siRNA oligoribonucleotides.

79-93. (Canceled)

94. (Previously presented) The composition of claim 34 wherein each of said first and second oligomeric compounds has from 21 to 24 nucleosides.

95. (Original) The composition of claim 34 wherein said first oligomeric compound is an antisense oligonucleotide.

96. (Original) The composition of claim 34 wherein said second oligomeric compound is a sense oligonucleotide.

97-103. (Canceled)

104. (Previously presented) The composition of claim 34 further comprising one or more overhangs.

105. (Canceled)

IX. EVIDENCE APPENDIX

Copies of Chiu *et. al.*, *RNA*, 2003, 9, 1034-1048 and Czauderna, *et al.*, *Nucleic Acid Res.*, 2003, 31(11), 2705-2716 are included on the following pages. These references were submitted to the Patent Office with in an information disclosure statement filed April 1, 2004. The Examiner returned an initialed copy of the PTO Form 1449 that accompanied the information disclosure statement to applicants' representative with an official action mailed May 5, 2006, confirming consideration of the references.

X. RELATED PROCEEDINGS APPENDIX

As discussed on page 3 of this appeal brief, notices of appeal and appeal briefs were filed for U.S. patent application numbers 11/054,848 and 10/860,265. The claims in those applications are directed to methods and compositions, respectively, that utilize certain double stranded oligomeric compounds. In response to the appeal brief filed for application number 11/054,848, the Examiner re-opened prosecution and issued a non-final official action containing a new ground of rejection on October 20, 2009. The Examiner also re-opened prosecution for application number 10/860,265 by issuing a non-final official action containing a new ground of rejection on October 22, 2009. Notices of appeal were again filed for each application on December 2, 2009.